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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,595	07/05/2000	Leena Peltonen	VOSS1130	1041

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,595	PELTONEN ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-38,41-53 and 55-67* is/are pending in the application.

4a) Of the above claim(s) *49-53 and 55-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-38,41-48 and 62-67* is/are rejected.

7)☒ Claim(s) *29 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DTAILED ACTION

Applicant's response filed 22 September 2003 as to amendment of claims 29-38, 41-46, 48 and 62, cancellation of claims 39-40 and 54, and addition of claims 63-67, and Applicants' request (filed 22 September 2003) for extension of time of three months have been entered. Of the pending claims 29-38, 41-53 and 55-67, claims 49-53 and 55-61 are withdrawn from consideration (see the previous Office action mailed 26 March 2003). Therefore, claims 29-38, 41-48 and 62-67 are examined in this Office action.

Please note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn, and that claims 1-28 are cancelled by the amendment filed 8 March 2000.

Objection to Specification/claims

The disclosure is objected to because of the following informalities:

The abstract of the disclosure is objected to because the abstract is too long in view of that abstract of a patent application should be generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. A single paragraph of 150 words or less commencing on a separate sheet following the claims is required. See MPEP § 608.01(b).

The response filed 22 September 2003 states that page 49 of the application as filed includes an abstract. Examiner, however, cannot find the corresponding page containing abstract thereof. Thus, submission of the abstract is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in page 19, the second paragraph (line 5 and lines 8-9). See also page 24, the first paragraph. Applicant is required to delete all embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

In claim 29 (the currently amended), "37 C" and "55 C" should be changed to "55 °C" and "37 °C", respectively. The corresponding correction should be made throughout the claims.

In claim 35 (the currently amended), "APECED" should be spelled out for the first recitation in the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-38, 41-43, 48 and 62-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of the full-length polynucleotide of SEQ ID NOs:1 and 6 and a method of producing polypeptides comprising expression of the polynucleotides encoding the polypeptides of SEQ ID NOs: 2 and 9 thereof (claim 48). Applicant is not in possession of (i)

any isolated polynucleotides comprising a nucleotide sequence comprising SEQ ID NOs: 1 and 6 (claims 29and 34); (ii) any the nucleotide sequences that are a mammalian homologs (claim 31) or murine homologs (claim 33); (iii) any variant polynucleotides that are structurally deviated from the full-length sequence of SEQ ID NO:1 and generated form mutagenesis, e.g., insertion, substitution, deletion and inversion (claim 35); (iv) any sub-sequence (i.e., fragments) that are only least about 0.94% sequence identity to the full-length polynucleotide SEQ ID NO:1 (see claim 41 language "an isolated fragment ...comprising at least about 21 nucleotide ...", wherein 21 nucleotides *versus* the full-length of SEQ ID NO:1 consisting of 2245 nucleotides gives rise to ~ 0.94% sequence identity thereof); (v) any polynucleotides complementary to nucleotide sequence or variant as indicated in (i) and (iii) (see claim 42); and (vi) any polynucleotide encoding a polypeptide having Cys4-His-Cys3 finger motifs (claim 67).

The current claim language encompasses a large number of the polynucleotide variants that are both structurally and functionally deviated from the claimed full-length APECED polynucleotide of SEQ ID NO:1. The claims of the instant application recite that the polypeptide encoded by APECED polynucleotide has the function of a transcription factor or transcription-associated factor (see claim 30). Yet, there are no factual evidence or/and sufficient teaching in this regard. Thus, applicants are not in possession of the polypeptide(s) encoded by the polynucleotide or sub-subsequence thereof which have the transcription factor activity or transcription-associated factor activity.

The specification is silent in description or/and working examples as to what is a loss of function or a gain of function with respect to mutants genetically or recombinantly made (claim

35). Thus, applicants are not in possession of any mutant polynucleotide molecules with respect to the biological function(s) of the APECED gene encoded protein.

The claims recite a "mammalian homologue" (claim 32) and "murine homolog" (claim 33) of the claimed polynucleotide. Note that the homologue represents a genus encompassing numerous analogs or derivatives of the claimed polynucleotides. Yet, the specification provides no description in this regard. Thus, applicants are not in possession of any polynucleotide sequences homologue to human polynucleotide of SEQ ID NO:1 or 6 from the mammals thereof. The factual sequence data in regard to the homology in respect to the SEQ ID NO:1 are needed for enablement.

Applicant has disclosed only the full-length polynucleotide of SEQ ID NOs:1 and 6; therefore, the skilled artisan cannot envision all the contemplated nucleotide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993).

Making changes from sub-sequence comprising from 21 nucleotides (or a portion or fragment, see claim 41) to the full-length SEQ ID NO:1 or 6 does not provide maintaining the same three-dimensional structure of the polypeptide encoded by the polynucleotide thereof as by the 100% identity over that of the full-length SEQ ID NO:1. The claim language of claims 29 appears to encompass any possible nucleic acid molecules that comprise SEQ ID NO:1; of them, many heterologous molecules would not have the same function of the claimed full-length

polynucleotide. And, claim 35 appears to encompass all possible mutations, including genetic mutations (e.g., allelic variants) as well as recombinant mutations (*e.g.*, insertion, deletion, substitution and inversion), which can be produced either *via in vitro* mutagenesis or *via* genetics, without concerning structure-function relationship. This would create numerous variants/mutants which biological activities are unpredictable. Applicants, therefore, are not possession of having any types of mutations of the claimed polynucleotide generated *via* protein engineering or by other mutagenesis approaches. Without characterization each polynucleotide mutant, the encoded polypeptide mutant thereof is unpredictable in view of structure and function. Because the specification fails to describe the consequence of the mutants and the common attributes or characteristics that identify any APECED mutant or establish any animal model regarding the therapeutic use of the mutant molecule for treating the APECED disease state, the specification is thus insufficient to enable skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

Furthermore, the claims of the present invention recite the hybridization conditions to SEQ ID NOs: 1 and 6, of which the hybridized polynucleotides are resulted from low stringency condition (see claim 32); such the claim language allows to include enormous sub-sequences/variants that are both structurally and functionally deviated from the full-length polynucleotide. The claim thus appears to include possibilities of annealing to the known polynucleotide molecule under low stringency condition would be unpredictably enormous. Quantity of the variants or mutants encompassed by the current claim language would be far beyond what can be predicted.

Also, applicants have amended claims to include the limitation, i.e., "wherein the nucleic acid molecule is identical in sequence to a portion of human chromosome 21q22.3, or a portion of a mammalian chromosome that share conserved synteny with human chromosome 21q22.3" (see claim 32); such the claim language encompasses numerous possibilities of any *structural arrangements* comprising the portion of the chromosome 21q, which is not enabling. Thus, applicants are not in possession of any portion of the chromosome 21q except the full-length sequences SEQ ID NOs:1 and 6.

Description of invention's reduction to practice, unaccompanied by any meaningful, distinguishing characteristics of evolved the polynucleotide mutants or mutants and use of the mutants or variants (e.g., in gene therapy, see page 13 of the specification) is insufficient to satisfy written description requirement of 35 U.S.C. §112, since inventors could have provided description of the mutant(s) or variant(s) of SEQ ID NO:1 polynucleotide, especially those produced by *in vivo* mutagenesis, since actual reduction to practice may demonstrate possession of embodiment of invention, but it does not necessarily describe what invention is, and since, in context of present case, disclosure of manner in which invention was reduced to practice does not satisfy more fundamental written description requirement set forth in Section 112.

The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient

to show that the applicants were in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the polynucleotide variants or/and mutants to describe its use in testing for a carriership for APECED or for a corresponding disease state (see page 1). Thus, Applicant was not in possession of the claimed polynucleotide variants/mutants or sub-sequences of the SEQ ID NO:1 which are produced from mutagenesis or screened from the hybridization, and not in possession of use of the same to recombinantly produce polypeptides thereof. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In consideration of the issued stated *supra*, the amount and level of experimentation needed is undue.

The response to the rejection under 35 USC, the first paragraph

The response filed 22 September 2003 argues that claim 29 has amended to include the defined hybridization condition which identifies numerous sequences that fall within the claim thereof (see the bridging paragraphs of pages 26-27) and to include the paired zinc finger motifs; thus, the claim is supported by enablement of the current disclosure. The argument is unpersuasive because of the reasons stated in the above ground of the rejection, and because (i) the hybridization condition will not distinguish between the polynucleotides encoding functional

and non-functional polypeptides; (ii) the Cys-His Cys motifs also exists in non-APECED polypeptide (see page 4 of the specification, line 5 from the bottom); and (iii) the asserted "numerous sequences" in the response (see above) are not commensurate with the enablement provided by the disclosure owing to the extremely large number of variant/sub-sequences encompassed by the claim. Since structure-function relationship of the variant/sub-sequences is unpredictable, absent factual indicia to the contrary, it would render the claims so broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

The response argues that claim 32 directed at mammalian homologs that is complementary to polynucleotide that hybridizes to SEQ ID NO:1 or 6 under low stringency condition that is identical to a portion of mammalian chromosome that shares conserved synteny with human chromosome 21q22.3, and that the specification provides numerous mammalian nucleic acid molecules that fall within claim 32 and sufficient disclosure to support the claim (see the last paragraph at page 27 and the first two paragraphs at pages 28). Also, the response asserts that, likewise, the specification has provided enablement to support claims 33 –34 (see page 28, the second paragraph). The applicants' argument is not persuasive because of reasons set forth in the above rejection and the followings. The low stringency has not yet been defined in the disclosure and refers to the condition that would pick up a extremely large number of variants or fragments (sub-sequences) which are not necessarily retain the same acuity of the full-length polynucleotides SEQ ID NOs: 1 and 6. In addition, the specification does not provide teaching or guidance as to how to make and use a portion of mammalian chromosome that shares conserved synteny with human chromosome 21q22.3; obviously, the said "a portion" of the

chromosome may or may not comprise the claimed APECED polynucleotide of SEQ ID NO:1 or 6. Thus, the claims do not meet the requirements set forth in 35 USC 112, the first paragraph regarding written description and enablement.

The response asserts that the mutations (insertion, deletion, substitutions and inversion) set forth in claims 35 is not directed to possible (a large number of) mutations of human polynucleotide (SEQ ID NO:1); rather, claim 35 incorporates functional elements that further define mutated versions of SEQ ID NO:1, e.g., claim 35 recites a hybridization condition (see page 28, the last paragraph), and that the polynucleotide of claim 35 is drawn to those sequences of mutated polynucleotides co-segregating with APECED, e.g., those mutants listed in Table 1 (see page 29, the first paragraph). Applicants' arguments are unpersuasive. The reasons for this have been stated above as well as below. The specification sets forth that the mutations (claims 35) results in a loss of function or a gain of function of polypeptide encoded by the claimed polynucleotide (see pages 7-8). Since the specification does not provide guidance or/and working examples as to how to make, characterize and use those mutations of loss-function thereof, the disclosure need to provide enablement to support the claimed subject matters. Note that the mutations set forth in Table 1 have no indication of their co-segregation with APECED. Moreover, the Table 1 mutations lack factual activity. Thus, the disclosure needs to provide sufficient written description in this regard.

Claim Rejections - 35 USC §112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30-31, 35-38, 41-43, 45-48 and 66-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 recites "... regulates or mediates transcription". Transcriptional mediator and transcriptional regulator are distinct compositions involved in mechanistically distinct processes. It is unclear as to how transcriptional mediator that is an object to be regulated by transcriptional factor(s) can act as regulator as well. The specification does not define this regard.

Claim 31 recites "wherein said polypeptide..."; there is no antecedent basis for this recitation in claim 35 from which claim 31 depends.

Claim 35 is indefinite in "...co-segregated with APECED" because autoimmue polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a disease or disorder state NOT a composition, i.e., the subject of co-segregated with the claimed polynucleotide must be a molecule or composition rather than a disease state. The dependent claims are also rejected.

Claim 36 recites "...4 nucleotides (CCTG) *normally* found at position 1086-1089" in SEQ ID NO:1; the recitation is indefinite in that the term "*normally*" renders claim ambiguous; Can CCTG sequence be found at different position other than the positions 1086-1089 thereof under certain circumstance? Also, claim 36 is vague in "a duplication of 4 nucleotides ....at position 1086-1089" since the segment consisting of nucleotides from position 1086 to 1089 only allows 4-nucleotide in length whereas the term "duplication" introduces an excess number of nucleotides.

Claim 41 is indefinite because the claims recites "at least about14 nucleotide" and the at least" is a narrower range than "about" which falls outside of this range.

Claim 48 recites "...producing a polypeptide of claim 29"; the recitation is indefinite because claim 29 is directed to polynucleotide NOT a polypeptide.

Claim 67 is unclear as to whether or the recitation " double paired finger motifs" refer to zinc finger or steroid finger motif or zinc finger-like motif (e.g., PHD-finger motif). Also, claim 67 is unclear in "Cys4-His-Cys3"; what do "4" and "3" refer to? Do they refer to cysteine at position 4 or position 3, or, total number of cysteine residues? Further, the claim is indefinite in "a protein that mediates and regulates transcription"; how can a protein factor *per se* is a component required for transcription that is an object of being regulated and simultaneously a regulator?

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C.

122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following are the new grounds of rejection

Claims 31-32, 35, 41-44, 62, 65 and 67 are rejected under 35 U.S.C. 102 (a) as being anticipated by Aaltonen J. et al. (*Genome Res.* (August, 1997) 7, 820-829).

Aaltonen et al. teach an isolated polynucleotide fragment (~a 350 kb) from human chromosome 21q22.3 associated with APECED (see page 821, the left column the second paragraph). Claim 32 of the instant application is directed to an isolated polynucleotide comprising the nucleotide sequence of a mammalian homolog of SEQ ID NO:1 wherein the nucleotide sequence is a portion of the chromosome that shares conserved synteny with human chromosome 21q22.3. Since the Aaltonen's polynucleotide is a *mammalian homolog* of SEQ ID NO:1 (an APECED associated gene) and *a portion* of said chromosome in which APECED gene resides, the above reference teaching meets the limitations set forth in the application claim 32.

Since the polynucleotide of the current invention is derived from chromosome 21q22.3 (see page 23), and since the DNA molecules taught by Aaltonen et al. are obtained from the same chromosome locus but different patients; of them, there must be polynucleotide(s) comprising single mutation which is capable of hybridizing to the application SEQ ID NO:1 sequence under the condition set forth in claim 35, the above Aaltonen et al. teaching is applied to claim 35 of the current application.

The Aaltonen et al. polynucleotide molecules are longer than 21 contiguous nucleotides and capable of hybridizing to the application SEQ ID NO:1, which meets the limitation set forth in the application claims 41-43.

Aaltonen et al. teach a primer for genotyping that encompasses hybridization to APECED gene, as applied to the application claim 44.

The isolated polynucleotide (~a 350 kb) by Aaltonen et al. must comprise the application SEQ ID NO:1 sequence. The reason for this is that the Aaltonen's polynucleotide fragment is (i) identified as a gene block associate with APECED, and (ii) isolated from human chromosome 21q22.3 locus (see page 826, the 2nd to the last paragraph and Fig. 4). Therefore, the Aaltonen reference is an anticipatory art over claims 62 and 65 of instant application.

Since the polypeptide encoded by the APECED gene should contain Cys(4)-His-Cys(3) type zinc finger motifs, the above Aaltonen et al. teaching is applied to claims 31 and 67 of the current application. Please note that the zinc finger motifs are inherent structural properties of the polypeptide thereof which will NOT be altered by process of isolating polypeptide thereof., or by isolating the polynucleotide fragment that encodes said polypeptide.

Claims 31-32, 35, 41-43, 62, 65 and 67 are rejected under 35 U.S.C. 102 (b) as being anticipated by Bjorses, P. et al. (*Am. J. Genet.* (1996) 59, 879-886).

Bjorses et al. teach an isolated polynucleotide segment (see "*Genomic DNA was extracted from ...*" at page 880, the right column the 3rd paragraph), which is derived from human chromosome 21q22.3 associated with APECED, and which segment is located between

the DNA makers D21S1225 and D21S171 (see Figure 1). The Bjorses et al. teachings meet the all the limitation set forth in claim 32 of the instant application.

Since the polynucleotide of the current invention is derived from chromosome 21q22.3 (see page 23), and since the DNA molecules taught by Bjorses et al. are obtained from the same chromosome locus but different patients; of them, there must be polynucleotide(s) comprising single mutation which is capable of hybridizing to the application SEQ ID NO:1 sequence under the condition set forth in claim 35, *i.e.*, ability of hebraizing to said sequence is inherent in Bjorses' polynucleotide, the above Aaltonen et al. teaching is therefore applied to claim 35 of the current application.

The Bjorses et al. polynucleotides are longer than 21 contiguous nucleotides and capable of hybridizing to the application SEQ ID NO:1, which meets the limitation set forth in the application claims 41-43.

Because the Bjorses' polynucleotide fragments are identified to be localized on human chromosome 21q22.3 wherein the APECED gene resides, and because, of isolated clones by Bjorses et al., there must be a polynucleotide comprising the application SEQ ID NO:1, the Bjorses reference is thus an anticipatory art over claims 62 and 65 of instant application. Note that the property of a polynucleotide comprising SEQ ID NO:1 is inherent in the above mentioned chromosomal locus, i.e., 21q22.3, and that segment(s) shown in Figure 1 should comprise SEQ ID NO:1 which is one of APECED associated genes (depending from the population being investigated, see abstract).

Since the polypeptide encoded by the APECED gene should contain Cys(4)-His-Cys(3) type zinc finger motifs, the above Bjorses's teaching is applied to claims 31 and 67 of the current

application. Please note that the zinc finger motifs are inherent structural properties of the polypeptide thereof, which will not be altered by process of isolating polypeptide thereof or by isolating the polynucleotide fragment that encodes said polypeptide.

Claims 32 and 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Korenberg J. R. et al. (US Pat. No. 6166180).

Korenberg et al. teach an APECED associated polynucleotide which is isolated from human chromosome 21 (see columns 3-4), wherein the polynucleotide is constructed in a BAC (bacterial artificial chromosome) comprising contig that contains APECED gene (see colun 4, lines 17-23). The Korenberg et al. teaching is therefore applied to claim 32 and 65 of the instant application.

The following is the rejection restated upon the current applicants' amendment

Claims 32, 35, 41-43 and 45-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Klinger, K. W. et al. (US Pat. No. 6071717).

Klinger et al. teach a human polynucleotide hybridizes to the polynucleotide of the current invention (see SEQ ID NO: 2 of the patent from nucleotides 1535 to 1564 which is complementary to the nucleotide sequence form nucleotides 2089 to 2118 of the SEQ ID NO:1 of the instant disclosure), which is a mammalian homolog of the application SEQ ID NO:1 polynucleotide and a portion of a mammalian chromosome having conserved synteny with human chromosome 21q22.3. Note that the application SEQ ID NO:1 is such the portion of the

chromosome having conserved synteny with the chromosome 21q22.3 to which Klinger's sequence is homologous. Thus, Klinger et al. teaching meets all the limitation set forth in the application claim 32.

Since the Klinger's sequence is a deletion version of SEQ ID NO:1 of the current application, the Klinger et al. anticipate claim 35 of the current application as well.

The above Klinger's teaching is applied to the application claims 41-43 because the portion of Klinger's sequence is larger than 21 nucleotides in length, which meets the limitation set forth in claim 41.

Also, Klinger et al. teach cloning the polynucleotide (the patent SEQ ID NO:2) into a vector (see the patent claims 1 and 7, and column 19) and a host (see the patent claim 9), e.g., bacteria, yeast and animal cells (see column 8, lines 40-55) *etc.*, as applied to the application claims 45-47.

The response to the rejection under 35 USC 102

The response filed 22 September 2003 argues that claim 35 is not anticipated by the Klinger et al. reference as (i) the claimed polynucleotide is co-segregated with APECED, (ii) the polynucleotide is located on chromosomal locus 12q22.3, and (iii) the Klinger's DNA molecule will not hybridize to SEQ ID NO:1 under the recited condition. The applicants' arguments are unpersuasive because of the following reasons. (1) Co-segregation with APECED gene is not inherent property of claim 35 polynucleotide, i.e., claim 35 does not recite the limitation regarding the claimed polynucleotide being co-segregated with APECED. (2) claim 35

(independent claim) does not recite the limitation as to a location on chromosome 21q22.3. And, (3) Since the office does not have a laboratory to test the reference molecule characteristics, it is applicant's burden to show that whether the Klinger's DNA molecules hybridize to SEQ ID NO:1 under the recited condition. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). The applicants are referred to see the corresponding rejection stated above.

Claim Rejections - 35 USC §103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Note the following is a restatement of the rejection in the previous Office action

Claims 29, 32, 34-35, 41-48, 62, 65 and 67 are rejected under 35 U.S.C. 103(a) as being obvious over Aaltonen, J. et al. (Genome Res. (August, 1997) 7, 820-829) taken with Bjorses, P.

et al. (*Am. J. Hum. Genet.* (1996) 59, 879-886) and Korenberg, J. R. et al. (US Pat. No. 6166180).

Aaltonen et al. teach localization of an autoimmune-polyendocrinophy-candidiasis-ectodermal dystrophy (APCED) gene in about 350 kb portion (see page 821, the left column) of human chromosome 21q22.3 using fiber fluorescence *in situ* hybridization (FISH), as applied to claims 29, 32, 35, 41-44, 62, 65 and 67 of the instant application.

Also, Aaltonen et al. teach primers used for genotyping the APECED gene (see "Methods" section), as applied to claim 44 of the current application.

Bjorses et al. teach localization of APCED gene in human chromosome 21q22.3 using linkage and haplotype analyses (see abstract and "Families and Methods" section), as applied to claims 29, 32, 34, 41-43, 62, 65 and 67 of the instant application. Also, by analyzing different populations (*human*), Bjorses et al. teach genetic basis of APECED which is directed to a spectrum of mutation in a gene (see the last sentence of abstract, and page 886), indicating that a mutated DNA molecules can hybridize to the application SEQ ID NO:1, which is applied to claim 35 of the current application.

Aaltonen et al. and Bjorses et al. do not explicitly teach vector, host and a method for use of the polynucleotide in production of the encoded polypeptide thereof.

Korenberg et al. teach chromosome 21 gene marker, an isolated polynucleotide in chromosome 21q22.3 region (see column 4, lines 28-47) wherein the APECED gene also resides, and teach a vector comprising the cloned polynucleotide (see column 8, lines 52-65) and a host cell, *e.g.*, mammalian cell, for expression of the polynucleotide (see column 7, lines 15-49). The

Korenberg teaching is applied to claims 44-47. Korenberg et al. teach that the polynucleotide is subject to substitution mutagenesis (see the bridging columns 7-8), as applied to the application claim 35. Also, Korenberg et al. teach a method for producing a polypeptide encoded by the polynucleotide (see column 7), as applied to the application claim 48.

Note that the above Korenberg's teaching is based on isolation of APECED associated polynucleotide from human chromosome 21 (see columns 3-4), wherein the polynucleotide is constructed in a bacterial artificial chromosome comprising contig that contains APECED gene (see column 4, lines 17-23), as applied to the application claims 29 and 35 form which claims 45-48.

One of ordinary skill in the art would have combined the teachings of the above references because (*i*) both Aaltonen et al. and Bjorses et al. teach localizing an APECED gene in human chromosome 21q22.3, provide a good basis for isolating the APECED gene, and indicate that APECED represents *a novel* gene locus (see the second last sentence, page 886 of Bjorses reference), (*ii*) Aaltonen et al. narrow down the region explored by Bjorses *et al.* to a 350 kb comprising the APECED gene, and (*iii*) Korenberg et al. teach a method of producing the gene product using an expression vector–host system.

When combined, there have been the advantages that the polynucleotide(s) isolated from APECED patients (populations) is of great interest since it would be useful for APECED gene identification and for facilitating diagnosing APECED disease state especially in Finnish and Iranian Jewish populations, as taught by Bjorses et al. (see page 886),

Thus, the skilled artisan would have been motivated to combine the above references to successfully arrive the current invention set forth in the claims *supra* as one is inextricably led to

the APECED gene sequence since Bjorses et al. has suggested use of positional cloning technique to isolate the gene, and, in fact, Aaltonen et al. teach use of the positional cloning (see abstract, and right column, page 825) in combination of FISH method for cloning the APECED cDNA. In order to obtain the gene product, the skilled artisan would also have adapted Korenberg's vector-host system to make the polypeptide encoded by the APECED polynucleotide including mutant(s). Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Thus, the above rejection is maintained.

The response to the rejection under 35 USC 103(a)

The response filed 22 September 2003 argues that the primary reference cited in the Office action, i.e., Aaltonen et al., does not disclose a polynucleotide of claims 29 or 35, form which the remaining rejected claims depend (see page 34, the 2nd paragraph). The applicants' argument is not persuasive because of the following reasons.

(i) The instant application identifies that the said polynucleotide is on the chromosome 21q22.3; thus, any reference teaching a DNA sequence associated with APECED would be an anticipatory art against the claimed invention.

And, (ii) Aaltonen et al. teach an isolated polynucleotide, which is located on human chromosome 21q22.3, and associated with APECED disease state, and a bacterial clone contig covering the DNA region critical for the cloning of the APECED gene (see page 821, the left column the second paragraph). In addition, Aaltonen et al. have identified the polynucleotide thereof as a portion of human chromosome 21q22.3 associated with APECED by genotyping,

which is about 350 kb (seepage 825, the right column, the first paragraph). Thus, the Aaltonen et al. teaching meets the limitation set forth in claim 29.

Likewise, Aaltonen et al. teaching anticipates claim 35. Since the DNA molecules taught by Aaltonen et al. are derived from the same chromosome locus but different patients; of them, there must be polynucleotide(s) comprising single mutation which would hybridize to the application SEQ ID NO:1 sequence under the condition recited in claim 35, the isolated DNA is thus applied to claim 35 of the instant application. Please note that the structural alteration is an inherent properties of Aaltonen et al. DNA clones (from various patients) and that since the office does not have a laboratory to test precise location of mutation in the polynucleotide thereof, it is applicant's burden to show the issue in this regard. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The response asserts that both Bjorses et al. and Aaltonen et al. are silent in structural features of the polynucleotide of claims 29 and 35 (see page 34, the last paragraph). As stated above, any reference teaching a DNA sequence associated with APECED would be a prior art against the claimed invention because the specification identifies that the subject polynucleotide is located in the chromosome 21q22.3. Thus, the applicants' argument is deemed unpersuasive.

Further, the response asserts that Korenberg et al. fail to teach the structure of the claimed polynucleotides and not qualified as an obviousness prior art (see page 35). The argument is not persuasive because Korenberg et al. teach an APECED-associated polynucleotide which is isolated from human chromosome 21q (see columns 3-4), wherein the polynucleotide is constructed in a bacterial artificial chromosome comprising contig that has APECED gene (see

column 4, lines 17-23), and because of the same reasons set forth *supra* (see above the immediate paragraph regarding the qualification of prior art (Bjorses et al. and Aaltonen et al.). Thus, the Korenberg teachings as to vector-host system for producing APECED gene product(s) are qualified for an obviousness prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

SWL

Samuel Wei Liu, Ph.D.

November 25, 2003